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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Patent Application of:
HORST PESCHEL

Conf. No.: 3984

: Group Art Unit: 1647

Appln. No.: 09/596,507

: Examiner: Robert Clinton Hayes

Filing Date: June 16, 2000

: Attorney Docket No.: 600574-1
(K400417US)

Title: Synthetic Neuronal Tissue Derived From Neuronal Progenitor Cells

DECLARATION OF JOHANNES SCHWARZ

I, Johannes Schwarz, declare and state as follows:

1. I am a founding member of NeuroProgen GmbH Leipzig, the assignee of the above-captioned patent application.

2. I am presently a full professor and vice-chairman of the department of Neurology at the University of Leipzig, Leipzig, Germany. I am also a visiting associate at the California Institute of Technology, Pasadena, California. I hold a degree in medicine from the medical school in Würzburg, and numerous professional certifications in the field of neurology, including Board Certification in Neurology and Neurophysiology, as listed in my *Curriculum vitae*, attached hereto as Exhibit A. I have also published extensively in peer-reviewed publications in the field. Publications representative of my work in the field are provided in Exhibit A.

3. I have reviewed

(i) this patent application,

- (ii) the Office Action mailed April 9, 2002 (Paper No. 9),
- (iii) the Office Action mailed December 5, 2002 (Paper No. 12),
- (iv) the Office Action mailed July 21, 2003 (Paper No. 16),
- (v) the Advisory Action mailed November 18, 2003 (Paper No.18).

4. I have reviewed the prior art references United State Patent No. 5,411, 883 of Boss, et al. ("Boss"), and International Patent Application No. WO 97/02049 of Luskin, *et al.* ("Luskin").

5. I am aware that the Examiner has rejected claims 44-49, 51-54, and 58-84 under 35 U.S.C. § 102(b) as being anticipated by Boss and Luskin, each taken individually. Paper No. 12 at 6. I understand that the Examiner contends that Boss teaches human and porcine neuronal progenitor cells, which the Examiner characterizes as "mammalian brain-derived neuronal tissue from the mesencephalon that inherently contain progeny of a single multipotent neuronal stem cell derived from immature stem cells." Paper No. 9 at 6. The Examiner further contends that Boss describes "partial differentiation," "full differentiation," and "select[ion of] individual cells expressing dopaminergic markers," in column 13 and 20. *Id.* The Examiner states that because there is no mention of graft rejection or provocation of an immune response, the cell cultures must not have contained glial cells. *Id.* The Examiner states that the neuronal progenitor cells of Boss are inherently "capable of differentiating." Paper No. 12 at 6. On these bases, the Examiner asserts the claims are anticipated by Boss. *E.g.*, Paper No. 12.

6. I am aware the Examiner has rejected claims 44-49, 51-54, and 58-84 as anticipated by Luskin. Paper No. 12 at 6. The Examiner states that Luskin teaches isolation of human and mammalian brain-derived neuronal progenitor cells that are "capable of differentiating into >90% dopaminergic neurons." He states that "Luskin's progenitor cells [sic] contain less than 2% glial cells," relying on the description on page 8, 11, and 21. Paper No. 9 at 7. According to the Examiner, "partial differentiation," "full differentiation," and "select[ion of] individual cells expressing dopaminergic markers," is described by Luskin at pages 12, 14, 16, and 29. On these bases, the Examiner asserts the claims are anticipated by Luskin. *E.g.*, Paper No. 12.

7. In this Declaration, I provide evidence to show that neither Boss nor Luskin teaches a neuronal tissue that is made of partially differentiated neural progenitor cells that (i) maintain the capacity to perform mitosis, (ii) differentiate substantially dopaminergic neurons upon contact with specific factors, and (iii) yet does not include a population of glial cells of sufficient number to provoke an immune response when implanted into a recipient.

The Boss Reference

8. Boss teaches cell culture methods for the proliferation of “neuronal progenitor cells” *in vitro* or for the terminal differentiation of those neuronal progenitor cells into dopamine-producing cells *in vitro* or post-implantation. Col. 3, ll. 35-43. The neuronal progenitor cells described in Boss are obtained from the dopaminergic system of the brain, from an area which, *in vivo*, differentiates into a relatively high concentration of TH-positive neurons. Col. 5, ll. 25-30. The cell cultures of the Boss invention have a “loci of undifferentiated cells and loci of neurons.” Col. 5, l. 53. Moreover, at least with respect to the monolayer cultures of the Boss invention, Boss teaches that, among the cells which differentiate into neurons, glial cells may also be observed. Col. 6, ll. 10-13. Boss also teaches that the neuronal progenitor cells of Boss may be induced to terminal differentiation into neurons by use of a differentiation agent that is sodium butyrate, butyric acid, cyclic adenosine monophosphate (cAMP) derivatives, phosphodiesterase inhibitors, adenylate cyclase activators and prostaglandins. Col. 13, ll. 35-50. Boss reports that upon completion of *in vitro* differentiation, the cell cultures contain “differentiated progenitor cells” that are no longer mitotic. Col. 13, ll. 66-68.

9. Moreover, the undifferentiated cell cultures of Boss are capable of differentiating into a variety of cells, such as glial cells, not just only dopaminergic neurons. In Col. 12, the passaging of neural epithelial cells is described. Under item 12, selection of specific cells using FACS or MACS is disclosed. Col. 12, ll. 53-63. Boss asserts “following growth of the neuron progenitor cell cultures for 5 -15 days, the cultures can be implanted.” However, the cell selection protocol would not give rise to cells that would differentiate substantially only into dopaminergic neurons; rather, the selected cells would still possess some capability of differentiating into at least more than one type of cell, including glial cells.

10. Boss also describes the *in vitro* differentiation of the progenitor cells. Col. 13, ll. 34 - Col. 14, l. 6. The cells are exposed to a differentiation agent to achieve a terminal differentiation. According to Boss, seven days of use of the differentiation agent is optimal. Col. 13, ll. 62-63. Thus, the cells are fully differentiated and lose their ability to undergo mitosis. In Example 8, *in vitro* induction of differentiation is described. Again, the cells are exposed to the differentiation agent for seven days. See Example 8, Col. 19, l. 37. The method of Example 8 yields cells that are fully terminally differentiated and are therefore not capable of undergoing mitosis.

11. Thus, Boss does not report the attempt of preparation or application of a cell culture of partially differentiated neuronal progenitor cells that maintain their capacity to perform mitosis and are capable of differentiating into substantially only dopaminergic neurons.

12. Boss teaches a cell culture method that includes development of a cell culture containing undifferentiated neuronal progenitor cells into a cell culture that contains either a larger population of undifferentiated neuronal progenitor cells or a cell culture that contains undifferentiated neuronal progenitor cells and terminally differentiated dopamine-producing cells.

The Luskin Reference

13. Luskin teaches a composition that is at least about 95% mammalian, non-tumor-derived, neuronal progenitor cells that express a neuron-specific marker and which can give rise to progeny which can differentiate into neuronal cells.

14. Luskin discloses that these neuronal cells are to be derived from the anterior sub-ventricular zone of the rat brain. Pg. 7 at ll 22-23. In rats, only a fraction of cells derived from the interior sub-ventricular zone will exclusively differentiate into cells that express neuronal markers (Davies and Temple, Nature 1994; 372:263-266). All of the examples given in Luskin relate to the isolation, proliferation, differentiation, and genetic modification, and transplantation of this type of rat cells.

15. Luskin teaches that the cells can be cultured and expanded, that they are capable of dividing *in vivo* after transplantation and that the Luskin composition is a source of dividing

cells having the characteristics of neuronal cells. Pg. 12, ll. 12-13; pg. 12, ll. 15-16; pg. 13, ll. 8-10, pg. 16, ll. 13-15.

16. Example 3 describes the culturing of cells and their differentiation after plating. Since, however, the cells have not been differentiated, they are not determined, and they would differentiate into a mixture of types of neuronal cells, *i.e.*, dopaminergic, gabaergic, cholinergic, etc. after transplantation. Thus, while each of these types of cells is a neuron or a neuronal cell, the compositions of Luskin are not substantially dopaminergic neurons.

17. The rat progenitor cells of Luskin demonstrate a rather high homogeneity of tissue, *i.e.*, they are neuronal cells, with few glial cells, and they possess some mitotic capability. They are different from the cells of the invention, however, with respect to homogeneity of cell type and the level of determination, *i.e.*, the degree to which the cells have descended along the differentiation. In my opinion, based upon my research and knowledge of the art, it is not possible and not reported that rat or human cells derived from the sub-ventricular zone can give rise to a progeny that differentiates predominantly into only dopaminergic neurons after, for example, transplantation.

Background of the Technology Related to the Invention.

18. A common definition of stem cells yet needs to be agreed upon. German law refers to stem cells that are “(i) capable of continuous self-renewal and (ii) give rise to cells of different tissue types.” This definition is in agreement with investigators (Garry et al., Curr Opin Nephrol Hypertens 2003;12:447-454)

19. “Neural progenitor cells” or “neural precursor cells,” as these terms are used in the art, are cells that can be expanded and are therefore capable of continuous self renewal. In addition, almost any publication relating to neural progenitor cells or neural precursor cells has shown that a clonal expansion of such cells and subsequent differentiation gives rise to at least two tissue types, neurons and glia (Uchida et al., Proc Natl Acad Sci USA 2000; 97:14720-14725). Neural progenitor cells or neural precursor cells would therefore fulfill the definition of stem cells. Thus, neural progenitor cells or neural precursor cells are also referred to within the art as “neural stem cells.”

20. The disadvantage of neural stem cells is that these cells are limited in their ability to differentiate solely into a desired specific cell type. For example, in the treatment of human disease, specific brain cells, *e.g.*, dopaminergic neurons to treat Parkinson's disease, are required. Therefore, it is important to modulate neural stem cells in such a way that they lose their stem cell character and become committed to differentiate only into one specific cell type, for example, dopaminergic neurons.

21. "Neuronal cells" and "neurons," as these terms are used in the art, are post-mitotic cells that have lost the capability of (continuous) self renewal. The loss of this capability (or the presence of the capability) is generally attributed to some as of yet unelucidated structural and/or chemical difference in the composition of the cell. As terminally differentiated cells, "neuronal cells" or "neurons" do not undergo mitosis. As a consequence, neuronal cells or neurons cannot be regarded as a source of cells for therapeutic applications such as transplantation, where expansion of the cell culture is necessary.

22. The invention of the present patent application is a new type of cell of a structural and/or chemical composition such that it is sufficiently committed to differentiate along only one pathway, such that the resultant terminally differentiated cells are solely of one type, *i.e.*, dopaminergic neurons. As is explained by the invention, the cells are prepared by transient exposure of pluripotent neural progenitor cells (stem cells that retain the structural and/or chemical structures that permit them to descend down two or more pathways of differentiation), to certain growth factors such as GDNF, LIF, IL-1, IL-11, and thyroid hormone. In preparing the patent application the cells of this invention have been referred to as "partially-differentiated neuronal progenitor cells" or "determined progenitor cells," a new terminology developed by the inventor to convey that the cells still remain capable of expansion some level of differentiation or commitment to a differentiation pathway had been developed. Thus, "partial differentiation" as used in this patent application is meant to express a reduction of pluripotency.

23. The "partially differentiated neuronal progenitor cells" differ from pluripotent neuronal progenitor cells in several aspects: They are structurally and/or chemically incapable of giving rise to more than one tissue type. They will differentiate into substantially only specific cell type, *e.g.*, dopaminergic neurons. Once determined, "partially differentiated neuronal

progenitor cells” respond to a treatment with a growth factor more rapidly than conventional pluripotent neuronal progenitor cells. When “partially differentiated neuronal progenitor cells” are exposed to a given growth factor, they do not give rise to glial tissue. In contrast, when pluripotent neuronal progenitor cells are exposed to the same growth factor, under the same conditions, the cells will, in part, differentiate into glial cells. Consequently, there is a chemical or structural aspect of the “partially differentiated neuronal progenitor cells” of the invention that is different from pluripotent neuronal progenitor cells of the prior art.

24. Moreover, the partially differentiated neuronal progenitor cells of the invention differ from terminally differentiated neuronal cells in at least that the cells of the invention are capable of undergoing mitotic division, and the terminally differentiated cells are not. This difference is a reflection of a physical and/or chemical difference between the cells, which, while as of yet unknown, does not render the difference any less significant.

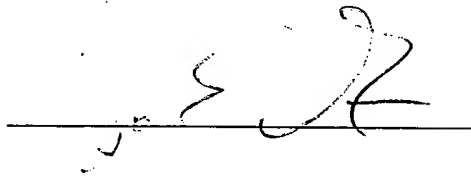
25. In addition, partially differentiated neuronal progenitor cells differ from terminally differentiated neuronal cells in that they are capable of continuous self-renewal. They maintain or gain their ability to perform mitosis in contrast the neural progenitor cells that have undergone terminal differentiation express genes related to neurogenesis or gliogenesis. During any given time of this differentiation process the self-renewing capacity is reduced compared to partially differentiated cells.

26. Thus, for at least these reasons, there is no technical or scientific basis supporting the Examiner’s contention that the cell cultures of Boss which contain undifferentiated cells (capable of differentiating into more than one type of cell and/or type of neuron) and terminally differentiated neuronal cells which no longer have the capability for mitosis, or the cells of Luskin, which are capable of differentiating into any type of neuronal cell, are the same as the cell tissue of the invention.

I declare that all statements made herein are of my own knowledge and are true and that all statements made on information and belief are believed to be true; and further, that those statements were made with the knowledge that willful false statements the like so made are punishable by fine or imprisonment, or both, under § 1003 of Title 18 of the United States Code,

and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

JOHANNES SCHWARZ

A handwritten signature in black ink, appearing to be 'J. Schwarz', is written over a horizontal line.

7153494



Johannes Schwarz, M. D.
Department of Neurology
University of Leipzig
Liebig str. 22a
04103 Leipzig
49-341-9724202
49-341-9724239

Curriculum Vitae

- | | |
|-------------------------|--|
| 1981-82 | Advanced studies (Violoncello, Vienna, Austria, Prof. André Navarra) |
| Nov. 1982-
Juni 1989 | Medical School in Regensburg (preclinical), Wuerzburg (clinical);
Louisville, KY and Boston, MA (clinical electives) |
| 1989 - 1996 | Residency and fellowships (movement disorders, clinical electrophysiology,
critical care neurology) at the Dept. of Neurology, University of Munich,
Klinikum Grosshadern (Chairman: Prof. Dr. Thomas Brandt) |
| 1996 | Board certification in Neurology |
| 1996 | Certification in Clinical Neurophysiology |
| 1996 - 1998 | Associate Professor of Neurology, University of Ulm, Germany
(Chairman: Prof. Dr. Albert C. Ludolph) |
| 1997 | Certification in „Intensive Care Neurology“ |
| 1998 | German Habilitation (venia legendi) |
| 1998 - 2001 | Visiting Associate in Biology, California Institute of Technology (Prof. Henry
A. Lester and Prof. Norman D. Davidson), sponsored by the Alexander-von
Humboldt-Foundation, Germany and the Huntington Medical Research
Institute, Pasadena |
| since 2001 | Professor and vice chairman, Department of Neurology, University of Leipzig
and visiting associate at the California Institute of Technology |
| 2000 | Richard-Heikkila-Award of the National Parkinson Foundation (Lester,
Labarca, Schwarz) |

Leipzig, January 2004

Peer review papers

1. Moessner J, **Schwarz J**, Fischbach W. Influence of "calcium²⁺-channel-blockers on exocrine pancreatic secretion by isolated rat acini. *Res Exp Med Berl* 1988; 188:255-265
2. Gupta M, **Schwarz J**, Chen XL, Roisen FJ. Gangliosides prevent MPTP toxicity in mice - an immunocytochemical study. *Brain Res* 1990; 527:330-334
3. Gasser T, **Schwarz J**, Trenkwalder C, Arnold G, Oertel WH. Apomorphin in der Therapie und Differentialdiagnose von Parkinson-Syndromen. In: *Verhandl. Dt. Ges. Neurol.*, Springer Verlag; 1991, Band 6, pp. 646-647
4. Oertel WH, Gasser T, **Schwarz J**, Arnold G. Klinik, Diagnose und Therapie der fokalen Dystonien - Einführung. In: *Verhandl. Dt. Ges. Neurol.*, Springer Verlag; 1991, Band 6, pp. 752-753
5. Tatsch K, **Schwarz J**, Oertel WH, Kirsch CM. SPECT imaging of dopamine D2 receptors with 123I-IBZM: initial experience in controls and patients with Parkinson's syndrome and Wilson's disease. *Nucl Med Commun* 1991; 12: 699-707
6. Gasser T, **Schwarz J**, Trenkwalder C, Poewe W, Oertel WH. Subcutaneous apomorphine in the differential diagnosis of Parkinson's disease. In: Agnoli A, Campanella G (eds), *New developments in therapy of Parkinson's disease*. John Libbey CIC, Roma; 1991, pp.
7. **Schwarz J**, Trenkwalder C, Arnold G, Gasser T, Oertel WH. Folinic Acid Therapy Fails to Improve Early Parkinson's Disease: A Two Week Placebo Controlled Clinical Trial. *J Neural Transm (PD section)*; 1992, 4: 35-41
8. **Schwarz J**, Tatsch K, Vogl T, Arnold G, Trenkwalder C, Kirsch CM, Oertel WH. Marked reduction of striatal dopamine D2 receptors as detected by 123I-IBZM-SPECT in a Wilson's disease patient with generalized dystonia. *Mov Disord* 1992; 7:58-61
9. **Schwarz J**, Tatsch K, Arnold G, Gasser T, Trenkwalder C, Kirsch CM, Oertel WH. 123I-Iodobenzamide-Spect predicts dopaminergic responsiveness in patients with de novo parkinsonism. *Neurology* 1992; 42:556-561
10. Oertel WH, Tatsch K, **Schwarz J**, Trenkwalder C, Scherer J, Weinzierl M, Kirsch CM. Reduction of striatal dopamine D2 receptors in 123I-IBZM-SPECT relates to neurological deficit in treated Wilson's disease. *Ann Neurol* 1992; 32: 743-748
11. **Schwarz J**, Tatsch K, Arnold G, Trenkwalder C, Ott M, Gasser T, Kirsch CM, Oertel WH: Die Bedeutung des Jodobenzamid-SPECT in der Differentialdiagnose und Behandlung des Parkinson-Syndroms. In: P. Fischer (Hrsg), *Editiones Roche*, Basel, pp 76-92
12. Gasser T, **Schwarz J**, Arnold G, Trenkwalder C, Oertel WH. Apomorphine test for dopaminergic responsiveness in patients with previously untreated Parkinson syndromes. *Arch Neurol* 1992; 49:1131-1134
13. Gasser T, Tatsch K, **Schwarz J**, Arnold G, Trenkwalder C, Oertel WH. Frühdiagnostik des Parkinson-Syndroms: Apomorphin-Test und IBZM-SPECT. In: *Morbus Parkinson und andere Basalganglienerkrankungen*. de Gruyter, Berlin, New York; 1992: 1-11
14. **Schwarz J**, Tatsch K, Arnold G, Ott M, Trenkwalder C, Kirsch CM, Oertel WH. 123I-Iodobenzamide-Spect in 83 patients with de novo parkinsonism. *Neurology* 1993; 43 Suppl. 6: 17-20
15. Tatsch K, **Schwarz J**, Kirsch CM. ZNS-SPECT: Rezeptorszintigraphie mit 123J-IBZM und 123J-Iomazenil. *Der Nuklearmediziner* 1993; 16:143-150
16. Baumert T, Kleber G, **Schwarz J**, Stäbler A, Lamerz R, Mann K. Reversible hyperkinesia in a patient with autoimmune polyglandular syndrome type I. *Clin Investig* 1993; 71:924-927
17. Arnold G, Bondy B, Bandmann O, Gasser T, **Schwarz J**, Trenkwalder C, Wagner M, Poewe W, Oertel WH. 3H-spiperone binding to lymphocytes fails in the differential diagnosis of de novo Parkinson syndromes. *J Neural Transm {P-D Sect}* 1993; 5:107-116
18. Oertel WH, **Schwarz J**, Tatsch K, Arnold G, Gasser T, Kirsch CM. IBZM-SPECT as predictor for dopaminergic responsiveness of patients with de novo Parkinsonian syndrome. *Advances of Neurology* 1993; 60:519-524
19. **Schwarz J**, Antonini A, Kraft E, Tatsch K, Vogl T, Kirsch CM, Leenders KL, Oertel WH. Treatment with D-penicillamine improves dopamine D2 receptor binding and T2-signal intensity in de novo Wilson's disease. *Neurology* 1994; 44:1079-1082

20. Arnold G, Trenkwalder C, Schwarz J, Oertel WH. Zotepine reversibly induces akinesia and rigidity in Parkinson's disease patients with resting tremor or drug induced psychosis. *Mov Disord* 1994; 9:238-239
21. Arnold G, Tatsch K, Oertel WH, Vogl Th, Schwarz J, Kraft E, Kirsch CM. Clinical progressive supranuclear palsy: differential diagnosis by IBZM-SPECT and MRI. *J Neural Trans* 1994; 42 Suppl.:111-118
22. Antonini A, Schwarz J, Oertel WH, Beer HF, Madeja UD, Leenders KL. 11C-raclopride and positron emission tomography in previously untreated patients with Parkinson's disease: influence of L-DOPA and lisuride therapy on striatal dopamine D2 receptors. *Neurology* 1994; 44:1325-1329
23. Schwarz J, Antonini A, Tatsch K, Kirsch CM, Oertel WH, Leenders KL. Comparison of 123I-IBZM-SPECT and 11C-raclopride-PET findings in patients with parkinsonism. *Nucl Med Comm* 1994; 15:806-813
24. Scherer J, Tatsch K, Schwarz J, Oertel WH, Kirsch CM, Albus M. Striatal D2 dopamine receptor occupancy during treatment with typical and atypical neuroleptics. *Biol Psych* 1994; 36:627-629
25. Scherer J, Tatsch K, Schwarz J, Oertel WH, Konjarczyk M, Albus M. D2-dopamine receptor occupancy differs between patients with and without extrapyramidal side effects. *Acta Psychiatr Scand* 1994; 90:266-268
26. Vogl Th J, Steiner S, Hammerstingl R, Schwarz J, Kraft E, Weinzierl M, Felix R. MRT der Leber bei Morbus Wilson. *Fortschr Röntgenstr* 1994; 160:40-45
27. Trenkwalder C, Stiasny K, Pollmächer T, Wetter T, Schwarz J, Kohnen R, Katzenwadi J, Krüger HP, Ramm S, Künzel M, Oertel WH. L-DOPA therapy of uremic and idiopathic restless legs syndrome: a double blind, crossover trial. *Sleep* 1995; 18:681-688
28. Trenkwalder C, Schwarz J, Gebhard J, Ruland D, Trenkwalder P, Hense HW, Oertel WH. Starnberg trial on epidemiology of parkinsonism and hypertension in the elderly: prevalence of Parkinson's disease and related disorders assessed by a door-to-door survey of inhabitants older than 65 years. *Arch Neurol* 1995; 52:1017-1022
29. Schwarz TF, Pfister HW, Schwarz J, Pauli C, Jäger G. Meningitis nach Aufenthalt im Mittelmeerraum, durch Sandfliegenvirus verursacht. *Nervenarzt* 1995; 66:789-791
30. Oertel WH, Trenkwalder C, Gasser T, Schwarz J, Bucher SF, Eichhorn T, Pogarell O, König G, Arnold G, Bandmann O, Dodel RC. Epidemiological, genetic, pharmacological, kinesiological, nuclear medical (IBZM-SPECT), standard and functional MRI studies on Parkinson's disease and related disorders and economic evaluation of Parkinson's disease therapy - clinical projects in the BMFT-research program Munich: "Parkinson's disease and other basal ganglia disorders". *J Neural Transm (PD section)* 1995; 46 Suppl:325-337
31. Gerlach M, Götz M, Dirr A, Kupsch A, Janetzky B, Oertel W, Sautter J, Schwarz J, Reichmann H, Riederer P. Acute MPTP treatment produces no changes in mitochondrial complex activities and indices of oxidative damage in the common marmoset ex vivo one week after exposure to the toxin. *Neurochem Int* 1996; 28:41-49
32. Schwarz J, Weis S, Kraft E, Tatsch K, Bandmann O, Mehrain P, Vogl T, Oertel WH. Signal changes on MRI and increase of reactive micro-, astrogliosis and iron in the putamen of two patients with multiple system atrophy. *J Neurol Neurosurg Psychiatry* 1996; 60:98-101
33. Schwarz J, Trenkwalder C. Restless Legs Syndrom: Therapie mit L-Dopa bzw. L-Dopa-Retardformen. *Aktuelle Neurologie* 1996; 23:26-29
34. Schwarz J, Oertel WH, Tatsch K. Iodine-123-iodobenzamide binding in parkinsonism: Reduction by dopamine agonists but not L-Dopa. *J Nucl Med*; 1996; 37:1112-1115
35. Eichhorn T, Gasser T, Mai N, Marquardt C, Arnold G, Schwarz J, Oertel WH. Computational analysis of automated handwriting movements: a rapid method to detect dopaminergic effects in Parkinson's disease. *Mov Disord* 1996; 11:289-297
36. Kupsch A, Sautter J, Schwarz J, Gerlach M, Riederer P, Oertel WH. N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity in non-human primates is antagonized by pretreatment with nimodipine at the nigral, but not at the striatal level. *Brain Res* 1996; 741:185-196

37. Antonini A, **Schwarz J**, Oertel WH, Pogarell O, Leenders KL. Long term changes of dopamine D2 receptors in patients with Parkinson's disease: a study with PET and [¹¹C]raclopride. *Mov Disord* 1997; 12:33-38
38. Scheidtmann K, **Schwarz J**, Holinski-Feder E, Gasser Th, Trenkwalder C. Paroxysmal choreoathetosis - a disorder related to Huntington's disease. *J Neurol* 1997; 244:395-398
39. **Schwarz J**, Scheidtmann K, Trenkwalder C. Improvement of motor fluctuations in patients with Parkinson's disease following treatment with high doses of pergolide and cessation of levodopa. *Eur Neurol* 1997; 37:236-238
40. **Schwarz J**, Planck J, Briegel J, Straube A. Single-fiber electromyography, nerve conduction studies and conventional electromyography in patients with critical-illness polyneuropathy: evidence for a lesion of terminal motor axons. *Muscle Nerve* 1997; 20:696-701
41. Tatsch K, **Schwarz J**, Mozley PD, Linke R, Pogarell O, Oertel WH, Fieber RS, Hahn K, Kung HF. Relationship between clinical features of Parkinson's disease and presynaptic dopamine transporter binding assessed with [¹²³I]IPT and single-photon emission tomography. *Eur J Nucl Med* 1997; 24:415-421
42. **Schwarz J**. Tremordominanter Morbus Parkinson: Therapie mit Dopamin-Agonisten. *Psycho* 1997; 23:446-449
43. Scherer J, Tatsch K, Albus M, **Schwarz J**, Mager T, Oertel WH. Dopamine D2 receptor occupancy during treatment with haloperidol decanoate. *Eur Arch Psychiatry Clin Neurosci* 1997; 247:104-106
44. Welz A, Pogarell O, Tatsch K, **Schwarz J**, Cryssagis K, Reichart B. Surgery of the thoracic aorta using deep hypothermic total circulatory arrest. Are there neurological consequences other than frank cerebral defects. *Eur J Cardiothorac Surg* 1997; 11:650-656
45. Plaschke M, **Schwarz J**, Dahlheim H, Backmund H, Trenwalder C. Cardiovascular and renin responses to head-up tilt test in parkinsonism. *Acta Neurol Scan* 1997; 96: 206-210
46. **Schwarz J**, Kornhuber M, Bischoff C, Straube A. Electromyography of the external anal sphincter in patients with Parkinson' disease and multiple system atrophy. *Muscle Nerve* 1997; 20:1167-1172
47. **Schwarz J**, Tatsch K, Gasser T, Arnold G, Oertel WH. 123I-IBZM binding predicts dopaminergic responsiveness in patients with parkinsonism and previous dopaminomimetic therapy. *Mov Disord* 1997; 12:898-902-
48. Kupsch A, Pogarell O, **Schwarz J**, Straube A, Oertel WH Tatsch K, Linke R. Parkinson's disease and tumor in the SMA, a re-evaluation. *J Neurol Neurosurg Psychiatry* 1997; 63:811-812
49. Arnold G, **Schwarz J**, Macher C, Oertel WH. Domperidone is superior to ondansetron in acute apomorphine challenge in previously untreated parkinsonian patients - a double blind study. *Parkinsonism & Related Disorders* 1997; 3:191-193
50. **Schwarz J**, Tatsch K, Gasser T, Arnold G, Pogarell O, König G, Oertel WH. 123I-IBZM binding compared to long term clinical follow up in patients with de novo parkinsonism. *Mov Disord* 1998; 13:16-19
51. Schwarz SC, **Schwarz J**, Sautter J, Oertel WH, Effects of macrophage migration inhibitory factor and macrophage migration stimulatory factor on function and survival of foetal dopaminergic grafts in the 6-hydroxydopamine model of Parkinson's disease. *Exp Brain Res* 1998; 120: 95 -103
52. Borasio GD, Linke R, **Schwarz J**, Schlamp V, Abel A, Mozley PD, Tatsch K. Dopaminergic deficit in amyotrophic lateral sclerosis assessed with [¹²³I] IPT-SPECT. *J Neurol Neurosurg Psychiatry* 1998; 65:263-265
53. **Schwarz J**, Scherer J, Trenkwalder C, Mozley PD, Tatsch K. Reduced striatal dopaminergic innervation shown by IPT and SPECT in patients under neuroleptic treatment: need for levodopa therapy? *Psychiatry Res: Neuroimaging* 1998; 83:23-28
54. Schwarz SC, Seufferlein T, Liptay S, Schmid RM, Kasischke K, Foster OJF, Daniel S, **Schwarz J**. Microglial activation in multiple system atrophy: a potential role for NF-kappaB/Rel Proteins. *Neuroreport* 1998; 9:3029-3032

55. Kraft E, Schwarz J, Gasser T, Arnold G, Pfluger T, Oertel WH. The combination of hypointense and hyperintense signal changes in the basal ganglia is specific for multiple system atrophy. *Arch Neurol* 1999; 56: 125-128
56. Schwarz J, Kraft E, Vogl T, Arnold G, Tatsch K, Oertel WH. Relative quantification of signal on T2-weighted MRI images in the basal ganglia: Limited value in differential diagnosis of patients with parkinsonism. *Neuroradiol*; 1999; 41: 124-127
57. Schwarz J. The value of single photon emission computed tomography in the diagnosis of neurological disorders. *Nervenheilkunde* 1999; 18: 71-74
58. Storch A, Ludolph AC, Schwarz J. HEK-293 cells expressing the human dopamine transporter are susceptible to low concentrations of 1-methyl-4-phenylpyridine (MPP+) via impairment of energy metabolism. *Neurochem Int* 1999; 35:393-403
59. Sperfeld AD, Collatz MB, Baier H, Palmbach M, Storch A, Schwarz J, Tatsch K, Reske SN, Joosse M, Heutink P, Ludolph AC. FTDP-17: An early-onset phenotype with parkinsonism and epileptic seizures caused by a novel mutation. *Ann Neurol* 1999; 46:708-715
60. Storch A, Kaftan A, Burkhardt K, Schwarz J. 1-Methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (salsolinol) is toxic to dopaminergic neuroblastoma SH-SY5Y cells via impairment of cellular energy metabolism. *Brain Res* 2000; 855:67-75
61. Schwarz J, Linke R, Kerner M, Mozley PD, Trenkwalder C, Gasser T, Tatsch K. Striatal dopamine transporter binding assessed by [¹²³I] IPT and single photon emission tomography in patients with early Parkinson's disease: Implications for a preclinical diagnosis. *Arch Neurol* 2000; 57:205-208
62. Storch A, Blessing H, Bareis M, Jankowski S, Schwarz J. Catechol-O-methyl transferase (COMT) inhibition enantio-selectively attenuates levodopa toxicity in primary dopaminergic neurons *in vitro*. *Mol Pharmacol* 2000; 57:589-594
63. Storch A, Kaftan A, Burkhardt K, Schwarz J. Cytotoxicity of 6-hydroxydopamine towards human SH-SY5Y dopaminergic neuroblastoma cells is independent from energy metabolism. *J Neural Transm PD Section* 2000; 107: 281-293
64. Eisensehr I, Linke R, Noachtar S, Schwarz J, Gildehaus FJ, Tatsch K. Reduced striatal dopamine transporters in idiopathic REM sleep behavior disorder: comparison to Parkinson's disease and controls. *Brain*; 123:1155-1160
65. Benamer TS, Patterson J, Grosset DG, Booij J, de Bruin K, van Royen E, Speelman JD, Horstink MH, Sips HJ, Dierckx RA, Versijpt J, Decoo D, Van Der Linden C, Hadley DM, Doder M, Lees AJ, Costa DC, Gacinovic S, Oertel WH, Pogarell O, Hoeffken H, Joseph K, Tatsch K, Schwarz J, Ries V. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [¹²³I]-FP-CIT SPECT imaging: the [¹²³I]-FP-CIT study group. *Mov Disord* 2000;15:503-510
66. Storch A, Burkhardt K, Ludolph AC, Schwarz J. Protective effects of riluzole on dopamine neurons: involvement of oxidative stress and cellular energy metabolism. *J Neurochem*. 2000 75:2259-2269.
67. Labarca, C., Schwarz J, Deshpande, P., Schwarz, S., Nowak, M.W., Fonck, C., Nashmi, R., Kofuji, P., Dang, H., Shi, W., Fidan, M., Khakh, B.S., Chen, Z., Bowers, B.J., Boulter, J., Wehner, J.M., and Lester, H.A. Point mutant mice with hypersensitive $\alpha 4$ nicotinic receptors show dopaminergic deficits and increased anxiety. *PNAS* 2001, 98:2786-2791
68. Chouker M, Tatsch K, Linke R, Pogarell O, Hahn K, Schwarz J. Striatal dopamine transporter binding in early to moderately advanced Parkinson's disease: monitoring of disease progression over 2 years. *Nucl Med Commun* 2001; 22:721-725
69. Storch A, Paul G, Csete M, Boehm BO, Carvey PM, Kupsch A, Schwarz J. Long-term proliferation and dopaminergic differentiation of human mesencephalon-derived neural precursor cells. *Exp Neurol* 2001; 170:317-325
70. Kupsch A, Sautter J, Götz ME, Breithaupt W, Schwarz J, Youdim MBH, Riederer P, Gerlach M, Oertel WH. Monoamine oxidase-inhibition and MPTP-induced neurotoxicity in the non-human primate: comparison of rasagiline (TVP 1012) with selegiline. *J Neural Transm* 2001; 108:985-1009

71. Storch A, Ott S, Hwang YI, Ortmann R, Hein A, Frenzel S, Matsubara K, Collins M, Ohta S, Wolf HU, Schwarz J. Selective dopaminergic toxicity of isoquinoline derivatives related to Parkinson's disease: studies using heterologous expression systems of the dopamine transporter. *Biochem Pharmacol* 2002; 63:909-920
72. Arnold G, Tatsch K, Kraft E, Bandmann O, Wächter T, Oertel WH, Schwarz J. Steele-Richardson-Olszewski syndrome: relation of dopamine D2 receptor binding and subcortical lesions in MRI. *J Neural Transm* 2002; 109:503-512
73. Storch A, Schwarz J. Neural stem cells and neurodegeneration. *Curr Opin Invest Drugs* 2002, 3:774-781
74. Arnold G, Tatsch K, Kraft E, Bandmann O, Wächter T, Oertel WH, Schwarz J. Steele-Richardson-Olszewski syndrome: Reduction of dopamine D2 receptor binding relates to the severity of midbrain atrophy in vivo - an IBZM-SPECT and MRI study. *Mov Disord* 2002; 17:557-562
75. Lehmensiek V, Tan EM, Schwarz J, Storch A. Expression of mutant alpha-synuclein enhances dopamine transporter mediated MPP+ toxicity in HEK 293 cells. *NeuroReport* 2002;13:1279-83
76. Blessing H, Bareiss M, Zettlmeisl H, Schwarz J, Storch A. Catechol-O-methyltransferase inhibition protects against 3,4-dihydroxyphenylalanine (DOPA) toxicity in primary mesencephalic cultures: new insights into levodopa toxicity. *Neurochem Int* 2003; 42:139-151
77. Schwarz J, Reichmann H. Parkinson's disease and neuroprotection: Dream or reality. *Akt Neurol* 2003; 30:51-58
78. Fonck C, Nashmi R, Deshpande P, Marks MJ, Riedel A, Schwarz J, Collins AC, Labarca C, Lester HA. Increased sensitivity to agonist-induced seizures and Straub tal in knock-in mice carrying hypersensitive $\alpha 4$ nicotinic receptors. *J Neurosci* 2003; 23:2582-2590
79. Eisensehr I, Linke R, Tatsch K, Kharraz B, Gildehaus JF, Wetter CT, Trenkwalder C, Schwarz J, Noachter S. Increased muscle activity during rapid eye movement sleep correlates with decrease of striatal presynaptic dopamine transporters. IPT and IBZM SPECT imaging in subclinical and clinically manifest idiopathic REM sleep behavior disorder, Parkinson's disease, and controls. *Sleep* 2003; 26:507-12
80. Gerhard A, Banati R, Goerres GB, Cagnin A, Myers R, Gunn RN, Turkheimer F, Good CD, Mathias CJ, Quinn N, Schwarz J, Brooks DJ. [^{11}C](R)PK11195 PET imaging of microglial activation in multiple system atrophy. *Neurology* 2003; 61:686-9
81. Rahman Z, Schwarz J, Wein M, Gold SJ, Kovoov A, Chen CK, Self D, Neve RL, Schwarz SC, Lester HA, Simon MI, Nestler EJ. RGS9 modulates dopamine signaling in the basal ganglia. *Neuron*. 2003; 38:941-52 (Rahman and Schwarz contributed equally)
82. Storch A, Lester HA, Boehm BO, Schwarz J. Functional characterization of dopaminergic neurons derived from murine mesencephalic stem cells. *J Chem Neuroanat* 2003; 26:133-42
83. Schwarz J. Rationale for dopamine agonist use as monotherapy in Parkinson's disease. *Curr Opin Neurol* 2003; 16 Suppl 1:S27-33
84. Milosevic J, Storch A, Schwarz J. Point of no return in spontaneously apoptotic mouse midbrain-derived neural stem cells. *Exp Cell Res*, in press
85. Günther P, Storch A, Schwarz J, Steinbach W, Sabri O, Wagner A, Hesse S.. Basal ganglia involvement of a patient with SCA 17 – a new form of autosomal dominant spinocerebellar ataxia. *J Neurol*, in press
86. Pöpperl G, Ruzicka E, Storch A, Gasser T, Tatsch K, Schwarz J. Comparison of α -dihydroergocryptine and levodopa monotherapy in Parkinson's disease: assessment of disease progression with [^{123}I]IPT SPECT. *J Neural Transm*, in press
87. Storch A, Hwang YI, Gearhart DA, Beach JW, Neafsey EJ, Collins MA, Schwarz J. Dopamine transporter-mediated cytotoxicity of β -carbolinium derivatives related to Parkinson's disease: relationship to transporter-dependent uptake. *J Neurochem*, in press
88. Orb S, Wieacker J, Labarca C, Fonck C, Lester HA, Schwarz J. Knock-In mice with L9'S $\alpha 4$ nicotinic receptors: substantia nigra dopaminergic neurons are hypersensitive to agonist and lost postnatally. Submitted to *Physiol Genomics*

89. Hermann A, Gastl R, Fiedler J, Liebau S, Popa MO, Boehm BO, Lerche H, Schwarz J, Brenner R, Storch A. Efficient generation of neural stem cells from adult human bone marrow stromal cells. Submitted to J Cell Sci
90. Schwarz J, Storch A, Pogarell O, Tatsch K. Striatal dopamine transporter binding in Parkinson's disease: follow up for 7.5 years. Submitted to NeuroImage
91. Koor A, Seyffarth P, Schwarz SC, Chen CK, Simon MI, Lester HA, Schwarz J. D2-dopamine receptors co-localize DEP domains and mice lacking the DEP domain containing protein, RGS9, develop dyskinesias associated with dopamine pathways. Submitted to J Neurosci